REMARKS / ARGUMENTS

The Office Action mailed May 12, 2006 has been received and reviewed. Applicants have amended the specification and claims as shown above, and offer the following remarks / arguments for consideration by the Examiner. Applicants respectfully request reconsideration of the application, as amended, and in view of these remarks and arguments.

PRIORITY

Applicants acknowledge with gratitude, the priority dates established by the Examiner on page 2 of the May 12, 2006 Office Action for the *in vivo* formation of a PRAK:ERK3 complex. However, Applicants respectfully disagree with the Examiner's assessment of the priority for the detectable *in vitro* formation of a PRAK:ERK3 complex.

Applicants note that U.S. Utility Patent Application 09/727,384 (filed December 1, 2000) and U.S. Provisional Patent Application 60/158,377 (filed December 2, 1999), upon which it is based, provide several passages describing the *in vitro* formation of protein complexes, such as PRAK:ERK3. For example, the Provisional Application states (on page 3, lines 10-14) that: "In a second embodiment, the ability to form a [protein] complex is assayed by measuring in vitro a complex formed by combining said first protein and said second protein." It also notes (on page 20, lines 24-26) that: "Protein interactions are detected in various systems including ...affinity chromatography ... and isolation of large molecular complexes." Further, it provides (on pages 20-21) that: "A cDNA encoding the desired protein is introduced in an appropriate expression vector and transfected in a host cell.... Purification of the expressed protein is achieved by conventional biochemical and immunological methods well known to those skilled in the art. The purified protein is then used for affinity chromatography studies: it is immobilized on a matrix and loaded on a column." etc. Finally, it includes a description of a method for the in vitro identification of modulators of protein-protein interactions in Example 34, on pages 35-36, using the interaction of PRAK and kendrin as an example. Although this example is specifically describes a method for screening for agents of the

PRAK:kendrin complex in vitro, the example concludes by specifically stating: "[c]andidate agents for modulating the ineraction of each of the protein complexes set forth in Tables 1-30 are screened in vitro in a similar manner," (U.S. Provisional Patent Application Serial No. 60/158,377, p. 36, ll. 3-4) and Table 9 (id. p. 7) discloses a protein complex comprising PRAK and ERK3.

In view of these teachings of U.S. Provisional Patent Application No. 60/158,377, Applicants respectfully submit that the priority for the detectable *in vitro* formation of a PRAK:ERK3 complex, should be accorded a date of December 2, 1999 – the filing date of U.S. Provisional Patent Application No. 60/158,377.

PRELIMINARY AMENDMENT

Applicants acknowledge with gratitude, the cancellation of claims 1-20, entry of new claims 21-37, and the correction of a priority date, as requested in the Preliminary Amendment filed on February 6, 2006.

INFORMATION DISCLOSURE STATEMENT

Applicants acknowledge with gratitude, the Examiner's consideration of the Information Disclosure Statement filed on February 6, 2006, and further acknowledge receipt of the executed copies of the submitted PTO/SB/08 forms submitted therewith.

TITLE

The original title of the application has been replaced at the request of the Examiner. The new title reads:

"PRAK:ERK3 PROTEIN COMPLEXES AND USE THEREOF"

Applicants believe that this new title satisfies the requirements set forth by the Examiner on page 3 of the Office Action mailed May 12, 2006. Should this assertion be incorrect, Applicants respectfully request further discussion of potential titles with the Examiner.

THE SPECIFICATION

Requirement for Additional Sequence Identifiers

Table 1 has been amended to introduce SEQ ID NOs for the amino acid sequences of the interacting proteins of the claims, which were previously described by their GenBank accession numbers. These amino acid sequences, and the nucleotide sequences of the nucleic acids that encode them, are further disclosed in an amended formal Sequence Listing, which is being provided concurrently with this response. Specifically, SEQ ID NO: 729 provides the nucleotide sequence of GenBank accession no. AF032437, which encodes PRAK; SEQ ID NO: 730 provides the amino acid sequence of PRAK, as listed in GenBank accession no. AF032437; SEQ ID NO: 731 provides the nucleotide sequence of GenBank accession no. X80692, which encodes ERK3; and SEQ ID NO: 732 provides the amino acid sequence of ERK3, as listed in GenBank accession no. X80692.

Applicants are also amending the specification to insert a paragraph necessary to incorporate by reference the amended formal Sequence Listing being provided concurrently herewith on Compact Disk. Applicants respectfully request that the amended Sequence Listing, and the paragraph directing its incorporation by reference, be entered into the application by the Examiner.

Applicants respectfully note that these amendments do not add new matter to the application, since the sequences associated with GenBank accession nos. AF032437 and X80692 were specifically referred to in Table 1 of the as-filed application. Applicants further note that inspection of the revision histories for the nucleotide and amino acid sequences associated with GenBank accession nos. AF032437 and X80692 reveals that the sequences associated with both of these accession nos. have not been altered since they were submitted directly to the NCBI on November 3, 1997 and July 28, 1994, respectively.

In view of the amendments made to Table 1 of the specification, and to the amended Sequence Listing provided concurrently herewith, Applicants respectfully submit that the application is in full compliance with 37 C.F.R. § 1.821.

Further Amendment of the 1st Paragraph

The first paragraph of the as-filed specification is being amended to uniformly present the dates of the related patent applications to which the instant application claims priority, using a "Month Day, Year" format. This paragraph is also being amended to correct an obvious error in the serial number of a provisional application to which the instant application ultimately claims priority. Specifically, the instant application is a continuation-in-part of U.S. patent application serial no. 10/035,343, which is related to U.S. Provisional patent application Serial No. 60/259,572 and NOT 60/259,571. The confusion over this provisional application likely resulted from the fact that both U.S. provisional patent application serial nos. 60/259,571 and 60/259,572 are in the line of priority for the instant application, and both were filed on January 4, 2001.

Applicants have also amended the priority section of the replacement Sequence Listing being provided concurrently herewith, to refer to U.S. Provisional patent application Serial No. 60/343,818, which was inadvertently omitted in the previously filed Sequence Listing.

Applicants believe that upon incorporation of this amendment to the first paragraph of the instant application that the list of related applications will be complete and accurate. Further, Applicants have carefully checked this amended list against both their own internal records, the corrected filing receipt issued for this application, and the official records of the USPTO found in the PAIR database, and no other discrepancies were found.

THE CLAIMS

Restriction / Election

Applicants acknowledge with gratitude, the cancellation of claims 1-20, and entry of new claims 21-37. Applicants confirm that claims 21-37 are pending in the application; that claims 29-37 are presently withdrawn from consideration as being drawn to a non-elected invention; that claims 21-28 are presently being examined on the merits; and that claims 21-28 and 29-37 are related as product and process of use. Applicants

recognize with gratitude, the Examiner's instructions regarding the proposed rejoinder of claims 29-37, should claims 21-28 be found to be in condition for allowance.

Utility

Applicants acknowledge with gratitude, the Examiner's reasoned conclusion (Office Action of May 12, 2006, p. 5) that the claimed invention has sufficient utility to meet the requirements under 35 U.S.C. § 101.

Present Amendments

Claim 21 has been amended as shown in the Listing of Claims by the addition of specific sequence identifiers, SEQ ID NOs:730 & 732, which refer to the amino acid sequences of PRAK and ERK3 previously defined by GenBank accession nos. AF032437 and X80692, respectively, and now provided in the amended Sequence Listing that is being filed concurrently herewith.

Provisional Double Patenting Rejection

Claims 21, 23, 24, 27 and 28 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over selected claims being prosecuted in copending U.S. patent application serial nos. 10/035,344; 10/194,385; 10/194,714; 10/194,966; 10/267,476 and 10/302,799. Further, the Office Action indicates that claims 21, 23, 24, 27 and 28 may be provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over selected claims in copending U.S. patent application serial nos. 10/639,017 (which probably should have been 10/639,067); 10/663,407; 10/859,063; 10/910,237; 10/979,642; 11/005,437; 11/033,462; 11/035,152; 11/041,102; 11/075,234 and 11/171,927.

The grounds for the provisional double patenting rejections (and potential provisional double patenting rejections) appear to stem from the Examiner's concern that the interacting proteins of the instant invention (PRAK and ERK3) are both kinases, and could conceivably share primary structure (i.e., amino acid sequence identity or

similarity) with other kinases. In light of these concerns, the Examiner has required Applicants to "identify applications that involve either the ERK3 and PRAK kinases of complexes claimed herein or other kinases disclosed to form complexes in protein-protein interactions, and to provide a copy of the pending claims so that the Examiner can determine if any double patenting does, in fact, exist."

As requested Applicants have reviewed the pending claims of all 17 applications named by the Examiner and have determined that: (a) none of the 17 applications pertain to protein complexes comprising ERK3 or PRAK, and (b) only U.S. patent application serial nos. 10/035,344 and 10/267,476 have pending claims directed to protein complexes comprising kinases of any sort. In the case of 10/035,344, which is a published application currently under appeal, the pending claims (provided herewith as Appendix A) are directed towards protein complexes comprising one of either of the two homologs of serine/threonine kinases known as "v-akt murine thymoma viral oncogene homologs 1 & 2" or "AKT1" & "AKT2." In the case of 10/267,476, Applicants note that this particular application, which has not been published and is currently under appeal, was filed along with a nonpublication request. In view of the fact that the confidentiality of this application would be compromised by the submission of copies of its pending claims in the instant response, Applicants must respectfully decline the Examiner's request in this case. (Applicants note that their action is consistent with 37 C.F.R. § 1.105(a)(iii), which only requires patent practitioners or assignees to provide copies of published applications.) However, in the spirit of cooperation, Applicants respectfully note that the requested information for application serial no. 10/267,476 is readily available to the Examiner, via the USPTO's "PAIR" database.

THE REJECTIONS

Claim Rejections under 35 USC § 112, 1st paragraph, Written Description

Claims 21-28 stand rejected under 35 USC § 112, first paragraph as being based upon a disclosure that allegedly lacks sufficient written description of the invention. Specifically, the Office Action (p. 9), which confirms and concludes that the specification

provides adequate written description for protein complexes comprising full-length PRAK interacting with full-length ERK3, and for protein complexes comprising a fragment of PRAK comprising amino acid residues 307-471 interacting with a fragment of ERK3 comprising amino acid residues 36-502 (as described in Table 1, p. 18), alleges that insufficient numbers of species are disclosed to support the full scope of claims directed to a genus of interacting proteins comprising fragment, homologues and homologues of fragments of PRAK and ERK3. The Office Action states (p. 9): "No other species are disclosed, suggested, or otherwise structurally described by teachings of the instant specification and neither the specification nor the claims indicate any distinguishing attributes that might be shared by the fragments and variants of the two genera of kinases which include numerous structural variants wherein a significant number of structural differences between genus members is permitted." The Office Action further states (p. 9-10): "The specification and claims provide no guidance as to what changes should be made to amino acid sequences of the specific, integral, PRAK and ERK3 kinase fragments indicated in Table 1 at page 18 and provide no common structural attributes with which to identify members of either genera."

As a first matter Applicants respectfully submit that the statement "The specification and claims provide ... no common structural attributes with which to identify members of either genera," is simply incorrect. The specification indicates (in Table 1 on p. 18) that primary structures of PRAK and ERK3 are as described in GenBank records with accession nos. AF032437 and X80692, respectively. Respectfully, the amino acid sequences found in these records inherently contain all possible fragments of the two interacting proteins. Thus, the specification, by reference to these GenBank records, provides the ultimate description of common structural attributes with which to identify ALL members of either genera of fragments – the primary structure of the full-length proteins. Apprised of the amino acid sequences found in these records, which have now been defined as SEQ ID NOs 730 and 732 and provided in the amended formal Sequence Listing being filed concurrently herewith, one of average skill in the art would be able to readily visualize any and all possible fragments of PRAK and ERK3. Further, Applicants respectfully assert that one of

average skill in the art of Molecular Biology could readily make any of these possible fragments they so choose, using routine methods of the art, and subsequently determine if that fragment retains the ability to interact with its corresponding partner protein, again using routine methods of the art. In so doing, one of average skill in the art could readily "map" the minimal interacting fragments of PRAK and ERK3, using only routine experimentation. Importantly, however, the artisan would never have been so motivated, had they not first learned from the instant application that these two proteins interact.

As a second matter, Applicants respectfully submit that the statement: "[N]either the specification nor the claims indicate any distinguishing attributes that might be shared by the fragments and variants of the two genera of kinases...," is also incorrect. Applicants respectfully note that the claims specifically state that fragments, homologues and fragments of homologues of PRAK must interact with ERK3 ("said second protein"). Likewise, the claims specifically state that fragments, homologues and fragments of homologues of ERK3 must interact with PRAK ("said first protein"). This functional requirement is a distinguishing attribute that has clear meaning to a skilled artisan, and serves to define the scope of the genus of interacting polypeptides.

Applicants note that the specification provides extensive description on methods for determining whether proteins interact, and determining whether specific fragments or homologues, or homologues of fragments retain the functional attribute (the ability to interact) that is required for them to fall within the scope of the claimed invention. Further, the specification provides extensive teachings on determining whether polypeptides are homologous, and on determining the level of sequence identity between two proteins, or protein fragments. Such teachings constitute aspects of the written description of the invention that have apparently been overlooked by the Examiner.

As a third matter, Applicants note that it is well-settled law that adequate written description can be provided by a combination of structural and functional characteristics, and that a single species can represent a genus when described by a combination of structural and functional characteristics. See, e.g. Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005), and discussions below. Applicants believe that through this combination of structural and functional characteristics they

have provided sufficient written description in the instant specification to convince one of skill in the art that they were in possession of the full scope of the invention, even though the specification provides only one pair of species of interacting fragments of PRAK and ERK3 (in Table 1, on p. 18). Applicants believe this to be so, because they are convinced that one of skill in the art of detecting protein-protein interactions, when apprised of the discovery that PRAK specifically interacts with ERK3, could readily determine whether any fragments, homologues and homologues of fragments of PRAK and ERK3 interact to form the protein complexes of the claimed invention, using routine experimentation that is not undue.

In support of their assertions, Applicants note that both the USPTO's own Written Description Guidelines, as well as recent decisions by the United States Court of Appeals for the Federal Circuit, confirm their contention that a single species is adequate to define a genus, if that genus is described by a combination of structural and functional characteristics, as discussed below.

Importantly, The United States Patent and Trademark Office (PTO) has issued guidelines for the examination of patent applications under the 35 USC § 112, first paragraph, written description requirement. These guidelines state that the written description requirement of 35 USC § 112, first paragraph, can be met by:

> "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Guidelines for Examination of Patent Applications under 35 USC § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001) (emphasis added) (hereinafter "Written Description Guidelines"). This standard was adopted by the United States Court of Appeals for the Federal Circuit in Enzo Biochem Inc. v. Gen-Probe, Inc. 424 F.3d 1276 (Fed. Cir. 2005). In University of Rochester v. G.D. Searle, 358 F.3d 916 (Fed. Cir.2004), the Federal Circuit reaffirmed Enzo's use of the PTO written description guidelines, and recently, the Federal Circuit reaffirmed and

applied the standard in Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005).

In Invitrogen, the patents-in-suit claimed a genetically modified reverse transcriptase (RT) in terms of two distinct functional attributes – namely DNA polymerase and RNase H activity. The disputed claims made use of these functional attributes to define a broad genus of modified RT polypeptides. Claim 1 of U.S. Patent No. 6,063,608 (the '608 patent) is representative. It reads:

> 1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

'608 patent, col. 19, lines 26-34 (claim 1) (emphasis added). As noted by the Federal Circuit, "[w]ith these patents Invitrogen thereby claims a compound (the polypeptide or genetically engineered RT) in terms of biological function (DNA polymerase and RNase H activity)." Id. at 1072 (emphasis added).

The '608 patent specification summarily provided only one single working example of an isolated RT polypeptide having DNA polymerase activity and substantially reduced RNase H activity as required in the claims at issue. See the '608 patent. Nevertheless, the Federal Circuit decisively affirmed the finding of the district court that the written description requirement was satisfied. Specifically, the Federal Circuit recognized that (1) the sequences of the RT gene family were known at the time of filing, and (2) the specification discloses methods of testing to determine that an enzyme comprising the disclosed amino acid sequence has the claimed functional features – DNA polymerase activity with substantially reduced RNase H activity. Invitrogen, 429 F.3d at 1073-4. The court distinguished Invitrogen from University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) and Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993) in that the RT protein and gene sequences in Invitrogen were

known in the art and that a single example of the claimed RT protein was provided in the specification. See Invitrogen, 429 F.3d at 1073-4.

The Federal Circuit's analysis in Invitrogen is applicable to the rejected claims at issue. Indeed, the facts in Invitrogen are directly analogous to the facts in the instant case. Appellant's claims are drawn to an isolated protein complex formed by the interaction between a native or modified human PRAK protein and a native or modified human ERK3 protein. See Claim 21. The Examiner apparently does not reject the aspect of protein complex formed by interacting native full-length human PRAK and native full-length human ERK3 proteins, nor does he reject to the protein complex comprising the fragments of PRAK and ERK3 found to interact by the inventors, and disclosed in Table 1. What the Examiner rejects are protein complexes comprising interacting first and second proteins, wherein said first or second proteins are fragments of PRAK or ERK3 [other than those disclosed in Table 1] that retain the ability to interact, or homologues of PRAK or ERK3 which are at least 75% identical to PRAK or ERK3 and retain the ability to interact, or fragments of homologues of PRAK or ERK3 that retain the ability to interact. Yet the modified proteins encompassed by the claims are directly analogous to the modified RT protein in the claims in Invitrogen, which were found to meet the written description requirement of 35 USC § 112, first paragraph.

Specifically, the modified PRAK protein in amended Claim 21 is defined by both a structural feature (SEQ ID NO: 730, or a fragment, homologue of 75% or greater identity, or fragment of a homologue thereof), and a functional feature (interacts with ERK3). Likewise, the modified ERK3 protein in Claim 21 is also defined by both a structural feature (SEQ ID NO: 732, or a fragment, homologue of 75% or greater identity, or fragment of a homologue thereof) and a functional feature (interacts with PRAK).

Like the RT protein of Invitrogen, both human PRAK and human ERK3 were well known proteins in the art at the time of filing. Orthologs of such proteins from other species were also known (See, e.g. New *et al., EMBO J.* 17:3372-3384 (1998), Zhu *et al., Mol. Cell. Biol.* 14:8202-8211 (1994), and Turgeon et al., Biochem. J. 346:169-175 (2000); which were provided with the IDS filed on February 9, 2006), and the nucleotide

and amino acid sequences of such orthologs were known in the art by the filing date of this application.

As in the case of the '608 patent of Invitrogen, the instant specification discloses an example of protein fragments capable of forming the claimed protein complex. See specification, Table 1, page 18. Moreover, the specification provides extensive descriptions of various methods for making the modified PRAK and ERK3 proteins and preparing protein complexes, as well as various assays for determining whether such modified proteins meet the claimed functional feature, i.e., the ability to interact.

Clearly, under Invitrogen, there is a sufficient written description in the specification for the modified proteins. Additionally, the rejected claims can be factually distinguished from Eli Lilly and Fiers because the PRAK and ERK3 proteins were known at the time of filing and Appellant's specification describes specific embodiments of the claimed invention. As such, Appellant's specification clearly meets the written description requirement under Invitrogen, while the findings of Eli Lilly and Fiers do not require a finding of lack of written description in the instant case.

Furthermore, the PTO's own Written Description Guidelines teach that a single species of polypeptide, disclosed through a combination of structural and functional attributes, is sufficient to describe a genus of related, variant polypeptides. See Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (2001). This is amply clear from the USPTO Revised Interim Written Description Guidelines Training Materials (hereinafter "USPTO Written Description Training Materials"). See USPTO Written Description Training Materials, http://www.uspto.gov/web/menu/written.pdf (last visited September 12, 2006).

In particular, Example 14 of the USPTO Written Description Training Materials deals with a hypothetical claim that reads: "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→ B." Example 14 further states that "[t]he specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. Id. at page 53. The specification indicates that procedures for making proteins with substitutions, deletions,

insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein." Id. at page 53 (emphasis added). There is a single species specifically disclosed in the specification that is within the claim scope, that species being SEQ ID NO:3. Nevertheless, it is held in the USPTO Written Description Training Materials that the written description requirement is met in this case. As indicated, this is because the structures the species of the genus possess a specific degree of identity to SEQ ID NO:3, and the specification provides disclosure of an assay for identifying members possessing the claimed function, i.e., the catalytic activity.

The instant case is directly comparable to the scenario described in Example 14 of the USPTO Written Description Training Materials. In the instant case, the inventors have discovered that two known proteins – human PRAK and human ERK3 – specifically interact to form protein complexes. In Example 14, a single protein exhibits a specific catalytic activity. For the purposes of comparison, in the instant case the activities attributed to the pair of interacting proteins – namely, the ability of PRAK to specifically interact with ERK3, and the ability of the ERK3 to specifically interact with PRAK – are analogous to the catalytic activity of the protein having SEQ ID NO:3 in the Example 14. In other words, in Example 14, the functional characteristic under consideration in the claim is catalysis (of the reaction of A→ B), whereas in the instant case, it is the ability to interact with a native protein (PRAK or ERK3, accordingly). In both cases, the respective activities can be determined by assays disclosed in the respective specifications. In addition, while one single novel amino acid sequence of the protein in Example 14 of the Training Material is disclosed in the specification as SEQ ID NO:3, the PRAK and ERK3 proteins in Appellant's case and their orthologs were known in the art at the time of filing. Moreover, Appellants' specification discloses examples (by amino acid sequences) of interacting fragments recited in the claims in Table 1. Further, various methods are well known in the art for making additional protein homologues and fragments and identifying those capable of interacting. Clearly, following the USPTO Written Description Guidelines, the Examiner should have found a sufficient written description for Appellants' claims.

Thus, consistent with Federal Circuit precedent, and mirroring the claim provided in Example 14 of the USPTO Written Description Training Materials, the presently rejected claims meet the requirements of 35 U.S.C. § 112, first paragraph, as being supported by adequate written description in the specification as filed. Therefore, Applicants respectfully request that the written description rejection of claims 21 through 28, under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections under 35 USC § 112, 1st paragraph, Enablement

Claims 21-28 stand rejected under 35 USC § 112, first paragraph as being based upon a disclosure that allegedly provides insufficient enablement for the full scope of the claims.

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention without undue experimentation. Ratheon Co. v. Roper Corp., 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). In order to establish a prima facie case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). That is, the Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. Id.

The issue of enablement of biotechnological inventions under 35 USC § 112, first paragraph, was recently addressed by the Federal Circuit in Invitrogen Corporation v. Clonetech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005). In Invitrogen, the Federal Circuit considered whether the as-filed disclosure sufficiently enabled a claim drawn to a modified reverse transcriptase (RT) encoded by a modified RT gene and having DNA polymerase activity and substantially reduced RNase H activity, as recited above.

Specifically, as discussed above, the claim is directed to a very broad genus of highly variant RTs. The modified RT gene is derived from a collection of diverse organisms, ranging from viruses to primate animals. The claim does not recite, nor even

mention, any sequence of nucleotides or amino acids, nor specific regions of the RT protein that are modified. Rather, the claimed RT is defined solely by functional limitations, specifically, as a modified reverse transcriptase having DNA polymerase activity and substantially reduced RNase H activity.

The patent specification in Invitrogen discloses two different M-MLV RT nucleotide sequences bearing deletion mutations, but only one was shown to encode a RT protein having the functional features of the claimed invention. Further, the specification provides no teachings on how to create modified RT protein bearing a point mutation that would have the claimed functional features.

Yet, the Federal Circuit unequivocally held that the enablement requirement is satisfied for the full broad scope of the claim. Specifically, the court noted that "Invitrogen's teaching regarding deletion mutation is sufficient" "as it fully teaches a mode of making the claimed invention," even though no teachings of point mutations were given and only one operative deletion mutation example was provided. Id. at 1070.

Here in Applicants' rejected claims, an isolated protein complex is defined as comprising two interacting polypeptides, which can be the native human PRAK and ERK3 proteins, or a modified form thereof. The modified proteins are further defined by structural similarity as well as the functional feature of interacting with native PRAK or ERK3.

Notably, as discussed above, the nucleotide sequences of the PRAK and ERK3 coding sequences were known in the art at the time filing, as were the amino acid sequences of the two proteins. The Examiner asserts that Applicants claims are not enabled as to the protein homologues and fragments. This is clearly incorrect in view of Invitrogen. Specifically, as noted above, orthologs of both PRAK and ERK3, i.e. naturally occurring PRAK and ERK3 proteins from non-human species were known in the art at the time of filing. Moreover, a specific example of protein fragments having the claimed features of the claimed invention is disclosed in the specification. See specification, page 18, Table 1. In addition, an ordinarily skilled person in the art would know how to make modified PRAK and ERK3 proteins having deletions, substitutions, insertions and/or additions by routine methods commonly practiced in molecular biology.

Such modified proteins can be homologues or fragments of the native proteins. Regardless, the specification is replete with explanations of methods for making such homologues and fragments. See e.g., specification, page 14, line 1 to 17 (examples of orthologs and homologues, and methods of making homologues); page 14, line 18 to page 15, line 13 (determining sequence identity); Section 2.3, pages 104 through 109 (methods of preparing protein complexes); Section 4, pages 117 to 124 (methods of detecting protein complexes); Section 5.3.1. pages 134 to 145 (two-hybrid assays); Example 1, page 196 to 197; and Example 4, page 199 to 201.

Furthermore, it is important to note that the rejected claims specify that the homologues meet certain structural similarity to the native proteins by sequence identity (having at least 75% sequence identity with a native PRAK or ERK3 protein). In addition, both the protein homologues and fragments must possess the capability to interact, a functional feature like that in the claims in Invitrogen. The specification also provides detailed descriptions of various assays for identifying those homologues and fragments satisfying such functional features. See e.g., specification, page 14, line 1 to 17 (examples of orthologs and homologues, and methods of making homologues); page 14, line 18 to page 15, line 13 (determining sequence identity); Section 2.3, pages 104 through 109 (methods of preparing protein complexes); and Section 4, pages 117 to 124 (methods of detecting protein complexes). Clearly, one skilled in the art reading, upon reading the specification would be enabled to make the homologues and fragments, and thus the claimed protein complexes of the instant invention, without undue experimentation.

For example, one of ordinary skill in the art upon reading the specification would recognize that only a portion of PRAK is required to facilitate interaction with ERK3. See specification, page 18, Table 1. Further, as noted above, the ordinarily skilled individual could, in fact, readily determine the minimal fragment of PRAK that retains the ability to interact with ERK3 using routine experimentation, as taught by the specification. (In fact such experiments were used by two research groups to map the interaction and activation domains of the two proteins, and the results have been reported in post-filing art; see Schumacher *et al., EMBO J.* 23:4770-4779 (2004) and *Seternes et*

al., EMBO J. 23:4780-4791 (2004); both of which were provided in the IDS filed February 9, 2006.) Once such minimal interacting fragments, or interaction domains, are identified, one of ordinary skill in the art would appreciate that amino acid changes in the native PRAK protein outside of the region would less likely affect binding of PRAK to ERK3.

Also, at the time of filing, it was a routine task for a skilled artisan to identify proteins homologous or orthologous to PRAK, and to align such proteins and identify regions of conservation. Amino acid changes outside the regions of conservation would less likely result in loss of capability of interacting.

Thus, at the time in instant application was filed, one of ordinary skill in the art would know how to (1) perform alignments of amino acid sequences of homologous proteins, (2) identify conserved amino acid residues, (3) introduce conservative changes to specific residues in regions of proteins not exhibiting significant conservation, and (4) test whether the engineered variant proteins are still capable of interacting. Further, it can be reasonably predicted that protein homologues and fragments can be identified meeting the structural and functional limitations in Appellant's claims.

The Examiner argues that undue experimentation would be required for an individual to make the fragments and homologues for the claimed invention. It is true that an extended time and effort might be required to identify all possible PRAK and ERK3 fragments and homologues within the scope of the claims. However, "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in the art." Falko-Gunter Falkner, et al. v. Inglis, et al., (Fed. Cir. 2006, 05-01324) (quoting Board Op.) "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." Johns Hopkins Univ. v. Cellpro., (Fed. Cir. 1998).

Only routine experiments are required to make and identify PRAK protein homologues and fragments capable of interacting with ERK3, and ERK3 protein homologues and fragments capable of interacting with PRAK. Further, the example fragments in Table 1 of the specification provide reasonable direction for experiments. The extensive disclosure in the specification on the various methods of making and identifying the protein homologues and fragments meeting the claim limitations, provides a significant amount guidance. With all of these, undue experimentation simply is not required on the part of a skilled artisan to practice the claimed invention, especially in view of the high level of skill nowadays in the art of molecular biology in engineering genes and proteins.

In presenting his arguments that the instant specification provides insufficient enablement, the Examiner cites the publication of Seffernick *et al.* (*J. Bacteriol.* 183:2405-2410 (2001)), and notes that this publication teaches that alteration of 9 amino acids out of a total of 475 amino acids of a deaminase, is sufficient to alter its substrate specificity and catalytic activity of the enzyme. While this finding is fascinating, it is not relevant to the issue of enablement in the instant case for at least two reasons: First, it does not involve either of the two interacting proteins of the instant invention. Second, it is specific to alterations in the catalytic activity of an active site of an enzyme, and is not related to the interaction and binding of one protein to another.

In view of the above arguments, Applicants contend that the as-filed specification provides sufficient enablement to support the full scope of the claimed invention, and therefore meets the requirement of 35 U.S.C. § 112, first paragraph. Consequently, Applicants respectfully request that the enablement rejection of claims 21 through 28 be withdrawn.

Claim Rejections under 35 USC § 112, 2nd paragraph, Indefiniteness

Claims 21-28 stand rejected under 35 USC § 112, 2nd paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner has rejected the claims on the basis that "independent claim 21 lacks sequence identifiers for the amino

acid sequences of the intended fragments of the PRAK and ERK3 kinases thus claim 21, and claims 22-28 depending therefrom, fail to point out and distinctly claim Applicants intended subject matter...." In deference to the rejection, Applicants have amended claim 21, and Table 1 of the specification to recite specific SEQ ID NOs for the amino acid sequences of PRAK and ERK3 previously defined by GenBank accession nos. AF032437 and X80692, respectively. In addition, Applicants have filed concurrently herewith an amended formal Sequence Listing, to which 4 sequences have been added. Specifically, SEQ ID NO: 729 provides the nucleotide sequence of GenBank accession no. AF032437, which encodes PRAK, SEQ ID NO: 730 provides the amino acid sequence of PRAK, as listed in GenBank accession no. AF032437, SEQ ID NO: 731 provides the nucleotide sequence of GenBank accession no. X80692, which encodes ERK3, and SEQ ID NO: 732 provides the amino acid sequence of ERK3, as listed in GenBank accession no. X80692.

As noted above, these amendments do not add new matter to the application, since the sequences associated with GenBank accession nos. AF032437 and X80692 were specifically referred to in Table 1 of the as-filed application, and since the sequences associated with both of these accession nos. have not been altered since they were submitted directly to the NCBI on November 3, 1997 and July 28, 1994, respectively.

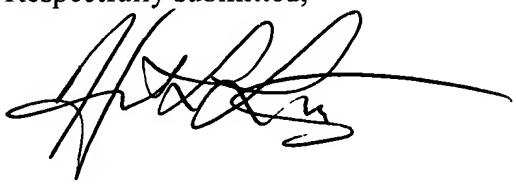
In view of the amendments made to claim 21 (and to Table 1 of the specification, and the amended Sequence Listing provided concurrently herewith), Applicants respectfully assert that, as suggested by the Examiner on page 13 of the Office Action, the rejection under 35 USC § 112, 2nd paragraph has been overcome. Applicants therefore respectfully request that the rejection of claims 21 through 28, under 35 USC § 112, 2nd paragraph, be withdrawn.

CONCLUSION

Applicants believe that once the amendments and arguments presented above are considered and entered into the record, the outstanding objection and rejections will be withdrawn, and the pending claims will be in condition for allowance. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is invited to contact the undersigned via his direct line (801-883-3463).

A petition for a one-month extension of time for the filing of this response is being filed concurrently herewith. Provisions for the payment of the necessary fee have been made in the petition. Therefore, it is believed that no other extension of time, or any additional fees are due with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees, or credit any over payment, to Deposit Account no. **50-1627**.

Respectfully submitted,



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